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TITLE: Randomized Phase II Trial of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma after Completion of Multimodality Therapy

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14. ABSTRACT

The Wilms' tumor gene, WT1, encodes transcription factors that regulate cell proliferation, differentiation, and apoptosis. WT1 protein is highly expressed in malignant pleural mesothelioma (MPM), and is a rational target for immunotherapy. We have developed a vaccine comprised of four WT1 heteroclitic peptides that are given together with Montanide and GM-CSF as immunologic adjuvants. This WT1 vaccine was previously tested in a small pilot trial, and shown to be safe and immunogenic. We have chosen to test the efficacy of this vaccine in MPM patients who have minimal disease burden after completion of multimodality therapy, but remain at exceedingly high risk for recurrence. The specific aim of this project is to conduct a multicenter, blinded, randomized trial comparing treatment with the WT-1 peptide vaccine + Montanide/GM-CSF to treatment with Montanide/GM-CSF alone in patients with MPM who have completed multimodality therapy. The primary endpoint is progression free survival. The trial has opened at Memorial Sloan-Kettering and is actively enrolling patients.

15. SUBJECT TERMS
Mesothelioma, WT1, vaccine

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INTRODUCTION:

The Wilms' tumor gene, WT1, encodes transcription factors that regulate cell proliferation, differentiation, and apoptosis. WT1 protein is highly expressed in malignant pleural mesothelioma (MPM), and is a rational target for immunotherapy. We have developed a vaccine comprised of four WT1 heteroclitic peptides that are given together with Montanide and GM-CSF as immunologic adjuvants. This WT1 vaccine was previously tested in a small pilot trial, and shown to be safe and immunogenic. We have chosen to test the efficacy of this vaccine in MPM patients who have minimal disease burden after completion of multimodality therapy, but remain at exceedingly high risk for recurrence. The specific aim of this project is to conduct a multicenter, double-blinded, randomized trial comparing treatment with the WT-1 peptide vaccine + Montanide/GM-CSF to treatment with Montanide/GM-CSF alone in patients with MPM who have completed multimodality therapy. The primary endpoint is progression free survival.

BODY:

This project has proceeded as indicated in the approved Statement of Work:

- The peptides were purchased, manufactured, and underwent sterility testing.
    - The peptides were ordered from AmbioPharm, Inc. Once produced, they were vialed under GMP conditions by University of Iowa Pharmaceuticals. The investigational agent completed sterility and stability testing to ensure safety for human use. The vials were delivered to the pharmacy at MSKCC.
- The protocol was reviewed by the various committees at MSKCC and the DOD leading to IRB approval.
    - Since IRB approval in September, 2010, the study has received approval from the FDA on 12/21/2010. During that time, the protocol was reviewed by the HRPO at the Department of Defense and several comments were made requiring changes to the protocol. The requested changes were made, reviewed by HRPO, and an amendment to the protocol was submitted to the IRB. The amendment was approved on 2/9/11. Final review took place by HRPO and an approval memo was issued on 2/11/11.
    - A start-up meeting was held with the research staff on 2/1/11 to inform all of the participants about the rationale, design, and logistics of this study.
- M.D Anderson Cancer Center is in the process of submitting the documents for the institutional review process at their center. Several conference calls have been held with M.D. Anderson to discuss various regulatory issues which seem to have been resolved at this point.
- Additional sites have not yet been recruited for participation in the study due to budget constraints.

KEY RESEARCH ACCOMPLISHMENTS:

- The planned randomized phase II trial is open at MSKCC and is actively accruing patients.

REPORTABLE OUTCOMES:

This protocol was highlighted in several presentations over the last few months which will hopefully increase exposure and ultimately enrollment. This includes:
ASCO, Chicago, IL - poster presented at Trials in Progress Session
Meso Symposium, Washington DC, slide presentation
World Conference on Lung Cancer, Amsterdam, slide presentation

CONCLUSION:

The clinical trial is open to enrollment at Memorial Sloan-Kettering which will continue for the next three years. Efforts continue to open the study at MD Anderson.

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Krug LM, Dao T, Brown AB, Maslak P, Travis W, Bekele S, Korontsvit T, Zakhaleva V, Wolchok J, Yuan J, Li H, Tyson L, Scheinberg DA. WT1 peptide vaccinations induce CD4 and CD8 T cell immune responses in patients with mesothelioma and non-small cell lung cancer, *Cancer Immunol Immunother*, 2010: 59(10):1467-79.

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Krug LM, Tsao AS, Kass S, Rusch VW, Travis WD, Panageas K, Adusumilli PS, Kris MG, Maslak PG, Scheinberg DA. Randomized, double-blinded, phase II trial of a WT1 peptide vaccine as adjuvant therapy in patients with malignant pleural mesothelioma. J Clin Oncol 29: 2011 (suppl; abstr TPS139)

APPENDICES:

ASCO abstract

SUPPORTING DATA:

None

TPS139 Trials in Progress Poster Session (Board #41A), Mon, 8:00 AM-12:00 PM

Randomized, double-blinded, phase II trial of a WT1 peptide vaccine as adjuvant therapy in patients with malignant pleural mesothelioma (MPM).

L. M. Krug, A. S. Tsao, S. Kass, V. W. Rusch, W. D. Travis, K. Panageas, P. S. Adusumili, M. G. Kris, P. G. Maslak, D. A. Scheinberg; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Texas M. D. Anderson Cancer Center, Houston, TX; Leukemia Service, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: The transcription factor, WT1, is commonly over-expressed in MPM and immunohistochemical tests for WT1 are used diagnostically. Certain WT1 peptides are processed and presented to the immune system and are thus an attractive target for T cell based immunotherapy. Using computer prediction analysis we designed analog peptides derived from WT1 sequences by substituting amino acids at key HLA-A0201 binding positions. We tested the safety and immunogenicity of a WT1 vaccine comprised of four peptides in patients with thoracic neoplasms expressing WT1 (Krug et al, Cancer Immunol Immunother, 2010). Six out of nine patients tested demonstrated CD4 T-cell proliferation to WT1 specific peptides, and all five HLA-A0201 patients tested mounted a CD8 T-cell response. One patient remains without progression $>$30 months after the start of the study. The median survival (measured from the date of the first vaccinations) was 13 months. Based on this pilot trial, we proposed a randomized phase II trial in a MPM patient population with minimal disease burden. **Methods:** Eligible patients will have MPM-expressing WT1 treated with combined modality therapy including surgery. Patients will be randomized to receive WT1 peptides plus Montanide adjuvant and GM-CSF, or Montanide and GM-CSF alone. The primary endpoint is progression free survival (PFS). 39 patients will be enrolled in each arm, which will provide 90% power to detect an improvement in PFS at one year from 50% to 70%. Immune responses will be evaluated using T cell proliferation assays, MHC tetramer staining and interferon-γ ELISPOT. Supported by grants from the Department of Defense (PR093640), NIH (Ca 23766,) and the Meso Foundation (MARF).